

New and Notable

Chromatin Control of Gene Expression: The Simplest Model

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Eukaryotes build their complexity by means of differential gene expression, often passed from mother to daughter cell in the form of another level of genetic coding called epigenetic marking. This selective silencing of parts of the genome is presumably carried out by specific aspects of the structure of the chromatin that makes up the chromosomes. How is this achieved?

The fundamental particle of chromatin structure is a self-assembled complex of basic histone proteins wrapped by approximately two turns of DNA (1). This unit called the “nucleosome” is the building block in a structure that compacts DNA of lengths on the order of meters into an $\sim 10\text{-}\mu\text{m}$ diameter cell nucleus. This packaging also acts to repress gene expression. Promoter sites tied up in nucleosomes are not easily accessible to factors that initiate transcription. Nucleosome density and folding of the chromatin both serve to control transcription, and special “remodeling factors” are needed to change chromatin structure and expose promoter sequences (2). The structure of chromatin is highly dynamic, changing with the metabolic activity of the cell (3).

A great deal is known about specific biochemical activities that alter chromatin structure and gene expression (4), but one can not help wondering whether there is some broad underlying polymer physics at work. The article by Zinchenko, Luckel, and Yoshikawa (5) in this issue approaches this problem

from an entirely different direction. This group has previously studied the physical chemistry of the association between cationic nanoparticles (models of the histone proteins) and DNA, mapping out rather complex phase diagrams as a function of particle size and concentration (6). The way in which positively charged nanoparticles tie up DNA is not obvious, and mechanisms change dramatically with particle size.

The question of what this means for gene expression is addressed in this article (5). The authors used fluorescently-labeled UTP to monitor transcriptional activity in vitro. They assembled compacted DNA using the T4 genome incubated with various sizes and concentrations of cationic nanoparticle and observed the fluorescence signal generated when the fluorescent label is released into bulk solution during RNA polymerization. Interestingly, the suppression of transcription does not correlate with the previously measured compaction in a simple way. Only the smallest (10-nm) particles allowed transcription to occur at intermediate loading densities. Larger particles shut transcription down rather abruptly. These smallest particles are comparable to nucleosomes in size, although the details of the DNA wrapping must surely differ considerably between real nucleosomes and these inorganic particles. The energetics have yet to be worked out properly, but presumably the 10-nm particles represent a compromise between reasonably good electrostatic binding and the need for enough mobility to allow rearrangements that permit the passage of RNA polymerase.

This work leads one to wonder about other simple physical mechanisms that might come into play. Gene expression

is known to be highly localized, with clusters of related genes often located in close physical proximity within the nucleus (7) (which is highly structured, albeit in a dynamic way (3,7)). How might this spatial order be maintained? One intriguing possibility (suggested to me by James Rothman of Columbia University) is that expressed RNA fragments tie up the DNA genome into a well determined three-dimensional structure by introducing crosslinks. Such DNA “Origami” is remarkably robust (8). This is just one other example of what we might learn from what biochemists might consider to be absurdly simple models of the nucleus; but sometimes, simple models can be very informative.

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